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(54) TRAITEMENT DES AIGREURS D'ESTOMAC
(54) HEARTBURN TREATMENT

(57)

The present invention is directed to the use of an alkali metal salt of a bicarbonate, preferably sodium bicarbonate, and an effective amount of a proton pump inhibitor in combination for the treatment of heartburn symptoms.

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The present invention is directed to the use of an alkali metal salt of a bicarbonate, preferably sodium bicarbonate, and an effective amount of a proton pump inhibitor in combination for the treatment of heartburn symptoms.

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(57) Abstract: The present invention is directed to the use of an alkali metal salt of a bicarbonate, preferably sodium bicarbonate, and an effective amount of a proton pump inhibitor in combination for the treatment of heartburn symptoms.

HEARTBURN TREATMENT

FIELD OF THE INVENTION

This invention discloses use of an omeprazole-bicarbonate combination for the treatment of heartburn, and acid indigestion.

BACKGROUND OF THE INVENTION

US patent, 5,840,737, Phillips, J. issued Nov 24 1998, describes a combination of a bicarbonate salt and omeprazole. The claims are directed to treatment of gastric acid disorders (unspecified) with a single dose of a pharmaceutical composition of omeprazole or lansoprazole together with a bicarbonate salt (Na or K preferred). The dose is orally administered as an aqueous solution or suspension.

The Philips patent focuses on the prophylactic prevention of upper GI bleeding in critically ill patients. It is particularly directed toward stress ulcer prophylaxis which has become routine therapy in intensive care units in most hospitals. An inherent advantage is the ability to infuse the solution via a nasogastric tube directly into the stomach. Data indicates that the omeprazole-bicarbonate solution/suspension combine the rapid onset of pH neutralization (due to bicarbonate) with the prolonged duration of effect of the proton pump inhibitor (PPI). There is an enhancement in time to onset of action of the PPI, omeprazole. This is postulated to reflect an effect of the bicarbonate to enhance the absorption of omeprazole. Indeed, in the presence of the bicarbonate omeprazole is observed to more rapidly become available systemically, and initial absorption of omeprazole is observed within 10-12 minutes in the combination as compared to 2-3 hours for omeprazole administered as enteric coated pellets.

However, Phillips does not suggest that the administration of a PPI plus a bicarbonate would be useful as a means to provide rapid onset, and prolonged duration of effect for relief of heartburn symptoms, nor in avoiding the reocurrence of heartburn symptoms.

Omeprazole has been formulated in many different embodiments such as in a mixture of polyethylene glycols as shown in U.S. Pat. No. 5,219,870 to Kim; U.S.

Pat No. 5,395,323 to Berglund discloses a device for mixing a pharmaceutical from a solid supply into a parenterally acceptable liquid form for parenteral administration to a patient.

U.S. Pat. No. 4,786,505 to Lovgren et al., discloses a pharmaceutical preparation containing omeprazole together with an alkaline reacting compound or an alkaline salt of omeprazole optionally together with an alkaline compound as a core material in a tablet formulation. The use of the alkaline material, which can be chosen from such substances as the sodium salt of carbonic acid, are used to form a "micro-pH" around each omeprazole particle to protect the omeprazole which is highly sensitive to acid pH.

The ability to provide a patient with a single dose administration of a preparation which has a rapid onset of acid neutralization would be a highly desirable dosage form for the treatment or prevention of heartburn symptoms.

SUMMARY OF THE INVENTION

The present invention is directed to a method of treating and/or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

The administration preferably consists of a single dosage without requiring further administration of a second dose of a bicarbonate salt.

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to single dose administration of a pharmaceutical composition for relief of heartburn symptoms. The term "heartburn symptoms" as used herein includes heartburn related to indigestion, sour stomach, upset stomach, episodic and co-incidental heartburn with meals, and heartburn related to gastroesophageal reflux of acid stomach contents. These are generally well recognized symptoms which are typically treated with, over-the-counter (OTC) medications, such as antacids, and more recently histamine H_2 receptor antagonists at reduced dosage. The treatments considered herein are the same as those symptoms for which various regulatory agencies, such as the FDA, have approved the use of H_2 receptor antagonists without prescription.

The present invention's use in the treatment of heartburn is a treatment which is safe, effective and useful for self-limiting gastrointestinal conditions. This

treatment is in contrast to the use of a proton pump inhibitor and an alkali metal bicarbonate salt for medically diagnosable gastrointestinal diseases, such as active duodenal ulcers, gastric ulcers, gastroesophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hypersecretory conditions such as Zollinger Ellison syndrome. The dosage administration is basically a once only treatment, and is not necessarily used for multiple daily dosing over a period of many days, weeks or long term duration, although it is recognized that it could be used as such.

Suitable proton pump inhibitors (PPI) useful in the present invention include those antisecretory compounds belonging to the class of compounds generally referred to as substituted benzimidazoles. Omeprazole is a substituted benzimidazole, 5-methoxy-2-[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl] sulfinyl]-1H-benzimidazole. Also suitable for use herein are the individual enantiomers, of omeprazole, such as the (S) isomer, or a suitable salt form, such as the calcium or magnesium salts, or a combination of both such as the (S) magnesium salt of omeprazole. Other substituted benzimidazoles suitable for use herein include, but are not limited to lansoprazole, 2-[[[3-Methyl-4-(2,2,2-trifluoroethoxy)-2-pyridinyl]methyl]sulfinyl]-1H-benzimidazole; pantoprazole, 5-(Difluoromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, and rabeprazole 2[[[4-(3-methoxypropoxy)-3-methyl-2-pyridinyl] methyl]sulfinyl]-1H-benzimidazole.

This class of compounds (the proton pump inhibitors) inhibit gastric acid secretion and do not exhibit anti-cholinergic or histamine H_2 antagonist properties. Drugs of this class suppress gastric acid secretion by the specific inhibition of the H< + > /K< + > ATPase enzyme system at the secretory surface of the gastric parietal cell.

Current use of proton pump inhibitors, particularly intravenous or oral liquid dosage forms is primarily directed towards medically diagnosable treatment of ulcers, or other medical determined mucosal bleeding of the gastrointestinal tract. Combinations of various H_2-antagonists, antacids and sucralfate are other currently used treatment options as prophylaxis for such damage.

These uses are however, not directed to the prevention or the treatment of heartburn symptoms.

Several buffered omeprazole solutions have been disclosed in publications, Andersson et al., Clinical Pharmacokinetics 24(1):71-8 (1993); Landahl et al. Clinical Pharmacokinetics 23 (6); 469-76 (1992); Andersson et al., Br. J. Clin. Pharmacol., 29(5):557-63 (1990); Regardh et al., Ther. Drug Monit. 12(2):163-72 (1990);

Andersson et al., Eur. J. Clin. Pharmacol., 39(2):195-7 (1990); and Pilbrant et al., Gastroenterol Suppl., 108:113-20 (1985).

All of the buffered omeprazole solutions described in these publications were administered orally and were given to healthy subjects who were able to ingest the oral dose. In all of these studies, omeprazole was suspended in a solution including sodium bicarbonate, as a pH buffer, in order to protect the acid sensitive omeprazole during administration. In all of these studies, the repeated administration of sodium bicarbonate both prior to, during, and following omeprazole administration were required in order to prevent acid degradation of the omeprazole given via the oral route of administration.

The bicarbonate was not given for its acid neutralizing capacity as an antacid, but for its use in preventing the degradation of the PPI. As a result, the ingestion of the large amounts of sodium bicarbonate and large volumes of water were required in contrast to the present invention. In these above-cited studies, as much as 48 millimoles of sodium bicarbonate in 300 ml of water were ingested in association with a a single dose of omeprazole for oral administration.

The present invention does not require the ingestion of excessive volumes of bicarbonate with water. Furthermore, the enhancement in onset of the PPI's action allows use of a minimal dose to achieve rapid and long-lasting relief of heartburn symptoms. The use of the combination of the PPI and bicarbonate permits using the PPI at dosages which are often suboptimal for standard Rx therapeutic applications (e.g., healing of duodenal or gastric ulcers, healing esophageal erosions, etc.). In the case of omeprazole, a dosage of about 10 to about 20 mg is desired.

Another aspect of the present invention is a dosage form of the omeprazole and bicarbonate which can be utilized to quickly make an omeprazole solution/suspension which is supplied in a solid form, such as in a powder form of a sachet, or as readily dispersible tablet or capsule. Alternatively the solid dosage form of omeprazole and bicarbonate, such as in a compressed tablet or capsule for oral ingestion may also be suitable, or even desired for use by the patient for the treatment of their heartburn symptoms.

An advantage of either the solution/suspension formulation or the solid dosage formulation are that both provide a means for the rapid onset and prolonged duration of effect for relief of heartburn symptoms and avoid the recurrence of these heartburn symptoms.

The pharmaceutical composition of the present invention may be prepared in accordance with Phillips, J., US Patent No. 5,840,737 whose disclosure is incorporated

herein by reference in its entirety. The composition may also be prepared by mixing omeprazole or other substituted benzimidazoles and derivatives thereof, with a solution including a bicarbonate salt of a Group IA metal. Preferably, omeprazole powder or granules, which may be enteric coated or not, are mixed with a sodium bicarbonate solution to achieve a desired final omeprazole concentration. The concentration of omeprazole in the solution/suspension can range from approximately 0.25 mg/ml to approximately 6.0 mg/ml. The preferred concentration for the omeprazole in the solution/suspension ranges from approximately 0.5 mg/ml to approximately 2 mg/ml.

The pharmaceutically acceptable alkali metal salt of a bicarbonate is preferably a Group IA metal salt, such as potassium or sodium. The concentration of the bicarbonate salt in the composition generally ranges from approximately 5.0 percent to approximately 60.0 percent. Preferably, the concentration of the bicarbonate salt ranges from approximately 7.5 percent to approximately 10.0 percent. In one embodiment of the present invention, sodium bicarbonate is the preferred salt and is present in a concentration of approximately 8.4 percent. A sufficient acid neutralizing capacity (ANC) amount is necessary and that will range from about 5 to about 40 ANC values, preferably from about 18 to 40 ANC values. It should be noted that the FDA considers an ANC value of 5 to be the minimum amount useful as an antacid. In the case of sodium or potassium bicarbonate preferred range is 18 to 40mEq, for calcium bicarbonate it is from about 36 to 80 mEq.

The amount of sodium bicarbonate used in the solution/suspension of the present invention is approximately 1 meq (or mmole) sodium bicarbonate per 1-2 mg omeprazole, with a range of approximately 0.75 meq (mmole) to 2.0 meq (mmole) per 1-2 mg of omeprazole, preferably 0.5 to 1.5mEq/1-2 mg of omeprazole.

In an another aspect of the present invention, enterically-coated omeprazole granules may be used and admixed with the sodium or potassium bicarbonate ($NaHCO_3$) solution which dissolves the enteric coating and forms an omeprazole solution/suspension for use in accordance with the present invention. Alternatively a solid dosage formulation of the enteric coated granules with the bicarbonate may be made and placed into capsules, or using the many techniques now known in the art, formulated into a compressed tablet.

Alternatively, micronized granules of a PPI, such as omeprazole may be used in place of conventional granules or powder. The process known as micronization is utilized in order to produce a particle having a smaller diameter. Micronization is the process by which solid drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size

increases the surface area, reducing the particle size increases the dissolution rate. Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

The formulation may contain suitable flavoring agents for use herein including, but not limited to, wintergreen, orange, grapefruit, chocolate, and cherry-raspberry. The amount of flavouring present in the formulation may be from about 0.1% to about 5.0% by weight of the composition.

The solid formulations may optionally contain suitable disintegrants such as, but not limited to, sodium starch glycolate [Explotab®], crosslinked polyvinylpyrrolidone, corn starch, acacia , Croscarmellose of sodium [Ac-di-sol®], sodium carboxymethylcellulose, veegum, or alginates. The amount of disintegrant present may be from about 1% to about 10.0% by weight of the composition.

The formulation may also include additional diluents or fillers which are preferably swellable agents, and may include, but are not limited to, various grades of microcrystalline cellulose, such as Avicel PH101, Avicel PH102, & Avicel PH200; corn starch; or Starch 1500. The amount of diluent or filler present in the formulation may be from about 1% to about 90.0% by weight of the composition.

The dosage form may also optionally contain suitable lubricants or wetting agents, such as but not limited to, magnesium stearate, stearic acid and its pharmaceutically acceptable alkali metal salts, calcium stearate, sodium stearate, Cab-O-Sil, Syloid, sodium lauryl sulfate, sodium chloride, magnesium lauryl sulfate or talc. Preferably, a suitable lubricant is magnesium stearate or stearic acid. Preferably, a suitable wetting agent is a surfactant, such as sodium lauryl sulfate. The amount of lubricant present in the formulation may be from about 0.1% to about 10.0% by weight of the composition, wherease the amount of wetting agent may be from about 0.1 – 20% by weight.

The formulation may also include additional binding agents, such as polyvinylpyrrolidone, (PVP), or Povidone 29K/32. The amount of binding agent present in the formulation may be from about 0.1% to about 30.0% by weight of the composition.

The formulation may also include coloring agents, or pigments, such as FD&C or D&C approved lakes and dyes, iron oxide and titanium dioxide. The amount of pigment present may be from about 0.1% to about 5.0% by weight of the composition.

Additional other conventional pharmaceutical diluents or excipients may also be included, as needed, in the admixture. Suitable excipients which may be employed include, for example, fillers, binders, lubricants, binders, compression aids, and wetting agents. To further assist patient compliance, the formulation may also contain sweeteners such as various natural sugars, aspartame, sodium cyclamate and sodium saccharinate; in addition to the flavorants. The amount of sweetner present may be from about 0.1% to about 20.0% by weight of the composition.

The formulations may also be manufactured in a concentrated form, such as an effervescent tablet, for oral administration upon admixture with water. Suitable effervescent formulations for use herein are well known in the art.

The following data illustrates the utility of the pharmaceutical composition of the present invention.

Comparison of onset of acid inhibition between omeprazole alone and the omeprazole – bicarbonate combination.

Khoury, *et al.* studied onset of acid inhibition following a single postprandial administration of omeprazole 10 or 20 mg in healthy volunteers. Khoury, et al., *Am. J. Gastroenterol.* ***93:*** 1619, (1998). The effect of omeprazole was compared with ranitidine, 75 and 150 mg. Gastric acid was measured via an intragastric pH probe. The design was a randomized crossover in 24 subjects. A standardized breakfast was consumed, drug was administered once intragastric pH returned to pH < 2.0, and intragastric pH recorded for 6 hr. Omeprazole, at both 10 and 20 mg failed to elevate intragastric pH to values ≥ 3.0 during the 6 hour postprandial recording period. In contrast, ranitidine 75 mg and 150 mg elevated intragastric pH > 3.0 within 178 and 145.5 min of dosing, respectively, and sustained pH > 3.0 for 2 and 3 hours of the recording period. Hence in this study, a single postprandial dose of 10 or 20 mg omeprazole had no effect on intragastric acidity for 6 hours following administration in healthy individuals.

Similarly, Decktor, *et al.* compared effects of single administrations of omeprazole 10 or 20 mg, famotidine 10 mg and placebo on meal-stimulated gastric acid secretion. Decktor, et al., *Am. J. Gastroenterol.* ***92:*** 1588, (1997). In a blinded, placebo-controlled cross-over study, each of 12 subjects randomly received the treatments one hour prior to intragastric infusion of a liquid peptone meal (600 ml 8% peptone, pH 4.0) designed to maximally stimulate acid output. Intragastric pH was maintained at pH 4.0 by continuous infusion of NaOH. Compared to placebo,

onset of significant acid antisecretory activity was observed 45 min, 75 min and 90 min following meal infusion for famotidine, omeprazole 20 mg and omeprazole 10 mg respectively. Over a 5 hr recording period. 10 mg famotidine reduced the amount of titrant required to maintain pH at 4.0 by 81%, while reductions of 56% and 27% were obtained with 20 mg and 10 mg omeprazole respectively. Famotidine 10 mg had a significantly faster onset of action and significantly greater antisecretory effect than omeprazole

The Phillips U.S. patent No. 5,840,737 in contrast, reports that single administration of bicarbonate + omeprazole elevates intragastric pH in critically ill patients from 3.0 ± 0.7 to 7.0 ± 0.6 within 2 hours after dosing. The dose was 20 mEq ANC provided by bicarbonate and a 40 mg omeprazole dose. Neutralization was then maintained by single daily administration of omeprazole (10 mEq ANC + 20 mg omeprazole) over the course of the study.

Lack of Effect of omeprazole in prevention of meal-induced heartburn

Decktor recently reported a single administration of omeprazole 10 or 20 mg failed to prevent meal-induced heartburn. Decktor, et al., *Am. J. Gastroenterol. 93:* 1614, (1998). 385 subjects with a history of food-induced heartburn participated in a single-dose, parallel, blinded, randomized, placebo-controlled trial. 60 minutes prior to receiving a standardized heartburn-inducing meal (chili and soft drink), subjects received either placebo, 10 mg famotidine (Pepcid AC), omeprazole 10 mg or omeprazole 20 mg. Subjects rated their heartburn symptom severity on a VAS scale beginning immediately prior to the meal, and at 30 min. intervals for 3 ½ hr postprandially. Compared to placebo, neither dose of omeprazole significantly prevented or reduced postprandial heartburn; 54, 52 and 55% of subjects treated with placebo, 10 mg omeprazole or 20 mg omeprazole reported moderate-to-severe post-prandial heartburn symptoms. In contrast, 34% of subjects treated with famotidine were heartburn free, and only 27% reported moderate to severe symptoms (consistent with previously published trials). 64% of subjects reported relief from 10 mg famotidine as good or excellent, compared to 40%, 42% and 47% treated with placebo, 10 mg omeprazole and 20 mg omeprazole, respectively ($p < 0.03$ vs. famotidine). Neither dose of omeprazole differed significantly from placebo for any efficacy parameter. This study showed a clear performance advantage for famotidine over omeprazole in prevention of meal-induced heartburn symptoms.

The present invention is directed to the recognition that a 10 or 20 mg dosage of omeprazole and a preferred acid neutralizing capacity of a bicarbonate salt is/will be sufficient to induce relief of heartburn symptoms without requiring additional dosing of the bicarbonate salt.

Study to prove effectiveness of a combination therapy in heartburn relief and prevention.

A suitable study involves administration of a provocative meal (chili, soft drink) to individuals who report suffering from meal-induced heartburn, and whose heartburn symptoms can be reproduced by the provocative meal and responds to antacid/acid neutralization treatment. Following development of heartburn, usually within 30 – 60 min of eating the meal, the combination of omeprazole and bicarbonate is administered in a randomized, blinded manner (10 – 20 mL containing 10 – 20 mEq (ANC) bicarbonate and 10 –20 mg omeprazole). Control treatments include bicarbonate alone, omeprazole alone, and placebo. Both the combination and bicarbonate treatments will provide rapid relief of heartburn symptoms, while lesser relief is attained with omeprazole and placebo (no difference between the latter treatments in degree of relief). A second heartburn provoking meal is then consumed at least 4 hours after the first meal, but no further treatments are administered. Those subjects who receive omeprazole-containing treatments after the initial meal experience a reduction in heartburn symptoms to the second meal. Subjects who receive antacid alone (bicarbonate) or placebo treatment with the first meal are expected to have fully recurrent symptoms to the later meal. Hence, the combination of bicarbonate + omeprazole provides for a rapid onset and a prolonged duration of heartburn relief.

All publications, including but not limited to patents and patent applications, cited in this specification are herein incorporated by reference as if each individual publication were specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The above description fully discloses the invention including preferred embodiments thereof. Modifications and improvements of the embodiments specifically disclosed herein are within the scope of the following claims. Without further elaboration, it is believed that one skilled in the are can, using the preceding description, utilize the present invention to its fullest extent. Therefore, the Examples

herein are to be construed as merely illustrative and not a limitation of the scope of the present invention in any way. The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows.

What is Claimed is:

1. A method of treating or preventing heartburn symptoms in a human in need thereof, which method comprises administering to said human a pharmaceutical composition comprising an effective amount of a proton pump inhibitor and an effective acid neutralizing amount of an alkali metal bicarbonate salt.

2. The method according to Claim 1 wherein the proton pump inhibitor is omeprazole, lansoprazole, pantoprazole, perprazole, or rabeprazole, or salts, isomers, enantiomers or derviatives thereof.

3. The method according to Claim 2 wherein the proton pump inhibitor is omeprazole.

4. The method according to Claim 3 wherein the dose of omeprazole is from about 10 to about 20mg.

5. The method according to any one of Claims 1 to 4 wherein the bicarbonate is sodium or potassium bicarbonate or a mixture thereof.

6. The method according to Claim 5 wherein the bicarbonate is sodium bicarbonate.

7. The method according to Claim 6 wherein the bicarbonate is administered in an ANC amount of about 18 to 40mEq.

8. The method according to Claim 1 wherein the proton pump inhibitor and alkali metal bicarbonate salt are administered in a solid unit dosage form.

8. The method according to Claim 8 wherein the dosage form is a compressed tablet.

9. The method according to Claim 8 wherein the dosage form is a capsule.

10. The method according to Claim 7 wherein the proton pump inhibitor is omeprazole and in a dosage range of from about 10 to about 20 mg.

11. The method according to Claim 1, wherein the pharmaceutical composition is a single unit dosage form administered in a volume of between approximately 10 ml and 20 ml of an aqueous solution.

12 The method according to Claim 11 wherein the dosage form is a sachet administered with water.

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(54) COMPOSITIONS PHARMACEUTIQUES D'UN INHIBITEUR DE LA POMPE A PROTONS NON GASTRO-RESISTANT AVEC UNE COMBINAISON DE SEL DE CARBONATE ET DE SEL DE BICARBONATE

(54) PHARMACEUTICAL COMPOSITIONS OF A NON-ENTERIC COATED PROTON PUMP INHIBITOR WITH A CARBONATE SALT AND BICARBONATE SALT COMBINATION

(57)

A method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal are disclosed. A presently preferred proton pump inhibitor is lansoprazole, a presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The composition is a fast-acting formulation which reduces the undesirable belching associated with proton pump inhibitor formulations that contain high doses of sodium bicarbonate.

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(54) Title: PHARMACEUTICAL COMPOSITIONS OF A NON-ENTERIC COATED PROTON PUMP INHIBITOR WITH A CARBONATE SALT AND BICARBONATE SALT COMBINATION

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A method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal are disclosed. A presently preferred proton pump inhibitor is lansoprazole, a presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The composition is a fast-acting formulation which reduces the undesirable belching associated with proton pump inhibitor formulations that contain high doses of sodium bicarbonate.

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(57) Abstract: A method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal are disclosed. A presently preferred proton pump inhibitor is lansoprazole, a presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The composition is a fast-acting formulation which reduces the undesirable belching associated with proton pump inhibitor formulations that contain high doses of sodium bicarbonate.

Pharmaceutical Compositions of a Non-Enteric Coated Proton Pump Inhibitor with a Carbonate Salt and Bicarbonate Salt Combination

Field of the Invention

The invention is directed to a method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal. A presently preferred proton pump inhibitor is lansoprazole, a presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The composition is a fast-acting formulation which reduces the undesirable belching associated with proton pump inhibitor formulations that contain high doses of sodium bicarbonate.

Background of the Invention

Lansoprazole is a substituted benzimidazole which inhibits gastric acid secretions. It belongs to a class of compounds called proton pump inhibitors (PPI). The key action mechanism of the PPIs is inhibition of H^+/K^+-adenosine triphosphate (also known as acid pump or proton pump), an enzyme present in the gastric parietal cells. These drugs are metabolized in the parietal cells to active sulfenamide metabolites that inactivate the sulfhydryl group of the proton pump, thus reducing the hydrogen ion secretion. Lansoprazole is a lipophilic weak base with poor aqueous solubility at low pH. It is unstable in low pH solutions and undergoes rapid acid-catalyzed degradation, though it is relatively stable at neutral or high pH.

Due to the pH sensitivity of lansoprazole described above, effective drug delivery is problematic, as the pH of the gastric environment is acidic and the pH of the intestinal region is relatively alkaline. For the drug to be therapeutically active after oral administration, it should be protected from the

acid present in the gastric juices. Further, the drug should reach the upper small intestinal region in an intact, absorbable form, where the drug can be rapidly absorbed to reduce acid production.

Enteric coating is by far the most popular method of protecting an acid-labile drug from gastric degradation. In this method, either the drug particles or the dosage form is coated with a polymer that does not dissolve in the low pH gastric environment, but dissolves in the alkaline environment of the small intestine. Currently, lansoprazole is administered as enteric-coated granules filled in a hard gelatin capsule in solid dosage form (B. Delhotal Landes *et al.* in "Clinical Pharmacokinetics of Lansoprazole", Clin. Pharmacokinet., 28 (6) 1995). This enteric coat dissolves at a pH > 6.

Tableted effervescent dosage forms of enteric-coated proton pump inhibitors including sodium carbonate and bicarbonate are disclosed in WO 97/25030 and U.S. Patent No. 6,132,770. In addition, U.S. Patent No. 5,840,737 discloses a pharmaceutical composition including an aqueous solution/suspension of omeprazole or other substituted benzimidazoles in a carrier including a bicarbonate salt of a Group IA metal.

However, there are some problems associated with enteric-coated preparations. These preparations are difficult to formulate as liquids, which may inconvenience pediatric patients or a patient population which has difficulty in swallowing. Moreover, the enteric coating must dissolve before the drug may be available for absorption. Since dissolution of the enteric coating is pH-dependent, and the pH profile of the gastrointestinal tract in an individual is variable at different times and is dependent on numerous physiological factors (e.g., the fed or fasted state), variable dissolution times for the enteric coat and variable pharmacokinetic profiles in individuals may result.

The acid-labile drugs for oral administration may also be protected from gastric acidity by neutralizing the pH of the gastric fluid. Conventional liquid formulations incorporate an acid neutralizer and enteric-coated PPI to create a stable formulation such as WO 94/02140, which discloses a core composed of an antacid combination and United States Patent No. 6,096,340 which discloses

an enteric-coated formulation containing omeprazole, a surface-active agent, a filler, a pharmaceutically acceptable alkaline agent and a binder.

Co-administration of enteric-coated omeprazole, another proton pump inhibitor drug (benzimidazole compound), with 8.4% sodium bicarbonate solution/suspension via the nasogastric tube, has been disclosed by Phillips *et al.* in "A Prospective Study of Simplified Omeprazole Suspension for the Prophylaxis of Stress-Related Mucosal Damage", Crit. Care Med, 1996, Vol. 24, No. 11, and Sharma *et al.* in "The Effects on Intragastric Acidity of Per-Gastronomy Administration of an Alkaline Suspension of Omeprazole", Aliment Pharmacol. Ther., 13:1091-1095 (1999). Before administering, the enteric-coated drug granules were shaken with the sodium bicarbonate solution for a sufficient time period until a milky white suspension resulted, to dissolve the enteric coating in the sodium bicarbonate solution. A large quantity of sodium bicarbonate must be administered with each dose of omeprazole, in the method described above. However, there is a major disadvantage in using large quantities of sodium bicarbonate orally, since sodium bicarbonate, upon neutralization in the gastric fluid, produces gases and results in belching (see *e.g.* U.S. Patent No. 5,840,737). This is detrimental to patients suffering from gastro-esophageal reflux disease.

In an attempt to reduce the amount of co-administered sodium bicarbonate, Phillips *et al.* (WO 00/26185) found that only 10 milliliters of an 8.4 % sodium bicarbonate solution were sufficient to provide effective acid neutralization and protect the enteric-coated omeprazole from degradation in the gastric environment. However, there is still a need for a method of PPI administration which is even more effective. In particular, a method which avoids the difficulties associated with the enteric-coating, yet still provides sufficient stability for either solid or liquid formulations would be particularly advantageous.

Brief Summary of the Invention

The invention is directed to a method for treating gastric acid disorders comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of at least one non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier; wherein said pharmaceutically acceptable carrier includes a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal.

The invention is also directed to a pharmaceutical composition comprising: at least one non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier; wherein said pharmaceutically acceptable carrier includes a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal.

In the method or the pharmaceutical composition of the present invention, either the Group IA metal of the bicarbonate salt or the Group IA metal of the carbonate salt, or both may be sodium or potassium. The non-enteric coated proton pump inhibitor may be a substituted benzimidazole or pharmaceutically acceptable salt thereof; and the substituted benzimidazole may be lansoprazole or a pharmaceutically acceptable salt thereof. The molar ratio of the bicarbonate salt to the carbonate salt is preferably one to one. A presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The pharmaceutically acceptable carrier may contain from about 125 mg to about 1000 mg of sodium bicarbonate; and from about 125 mg to about 1000 mg of sodium carbonate.

The invention is also directed to a method for treating gastric acid disorders comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of non-enteric coated lansoprazole or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable carrier; wherein said pharmaceutically acceptable carrier includes an equimolar ratio of sodium carbonate to sodium bicarbonate.

The invention is also directed to a non-enteric coated lansoprazole composition consisting essentially of: a) lansoprazole without enteric coating;

b) a bicarbonate salt of a Group IA metal; and c) a carbonate salt of a Group IA metal.

Detailed Description of the Invention

The invention is directed to a method for treating gastric acid disorders with a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal; and a pharmaceutical composition of a non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier including a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal. A presently preferred proton pump inhibitor is lansoprazole, a presently preferred bicarbonate salt is sodium bicarbonate, and a presently preferred carbonate salt is sodium carbonate. The composition is a fast-acting formulation which reduces the undesirable belching associated with proton pump inhibitor formulations that contain high doses of sodium bicarbonate. Detailed discussions of the compositions and methods follow.

The Compositions

The compositions include a proton pump inhibitor and a combination of a carbonate salt and a bicarbonate salt. The metal cation can be the same for the carbonate salt as well as the bicarbonate salt, or the metal cation on the carbonate salt can be a different one from the metal cation on the bicarbonate salt. The molar ratio of the carbonate salt to the bicarbonate salt can be from about 75:25 to about 25:75; or preferably from about 60:40 to about 40:60. The most preferred combination of carbonate salt and bicarbonate salt is an equimolar mixture of sodium carbonate and sodium bicarbonate, referred to as "carbicarb". Substitution of carbicarb for bicarbonate in proton pump inhibitor formulations has certain advantages: 1) carbicarb results in a reduction in carbon dioxide by-product upon neutralization by gastric acids; 2) due to the higher acid-neutralizing capacity of carbonate ions than bicarbonate ions, less of the combination is required for gastric acid neutralization. These advantages translate to more effective proton pump inhibitor formulations, as the decrease in carbon dioxide by-product means that undesirable belching subsequent to

administration will be reduced, and since less neutralizing agent is required, a smaller pill may be formulated. Moreover, we have found that the amount of carbicarb to be utilized is dependent upon the conditions of the stomach, and is unrelated to the amount of proton pump inhibitor to be administered. In most compositions, between 250-2000 mg of carbicarb is sufficient with each dose of proton pump inhibitor.

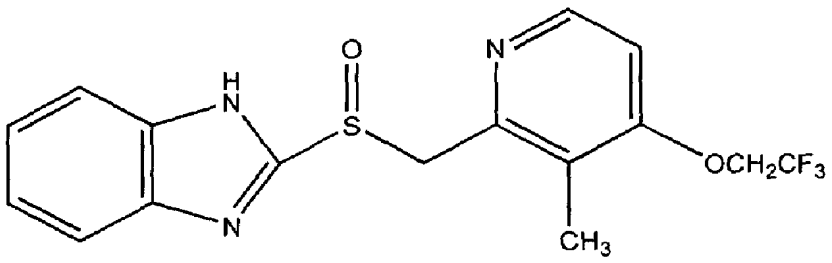
The phrase "Group IA metal" as used herein describes lithium, potassium and sodium.

The phrase "bicarbonate salt" refers to a compound of the formula $M^+HCO_3^-$, wherein M^+ is a Group IA metal as defined above. A presently preferred bicarbonate salt is sodium bicarbonate, $NaHCO_3$.

The phrase "carbonate salt" refers to a compound of the formula $(M^+)_2\ CO_3^{-2}$, wherein M^+ is a Group IA metal as defined above. A presently preferred carbonate salt is sodium carbonate, Na_2CO_3.

Proton pump inhibitors include substituted benzimidazoles such as omeprazole, lansoprazole, pantoprazole, pariprazole and leminoprazole.

A presently preferred proton pump inhibitor is lansoprazole, shown below.



The proton pump inhibitors of the present invention can be used in the form of pharmaceutically acceptable salts derived from inorganic or organic acids. The phrase "pharmaceutically acceptable salt" means those salts which are, within the scope of sound medical judgement, suitable for use in contact with the tissues of humans and lower animals without undue toxicity, irritation, allergic response and the like and are commensurate with a reasonable benefit/risk ratio. Pharmaceutically acceptable salts are well-known in the art.

For example, S. M. Berge *et al.* describe pharmaceutically acceptable salts in detail in J. Pharmaceutical Sciences, 1977, 66: 1 *et seq*. The salts can be prepared *in situ* during the final isolation and purification of the compounds of the invention or separately by reacting a free base function with a suitable organic acid. Representative acid addition salts include, but are not limited to acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphor sulfonate, digluconate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxyethansulfonate (isothionate), lactate, maleate, methane sulfonate, nicotinate, 2-naphthalene sulfonate, oxalate, palmitoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, phosphate, glutamate, bicarbonate, p-toluenesulfonate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; arylalkyl halides like benzyl and phenethyl bromides and others. Water or oil-soluble or dispersible products are thereby obtained. Examples of acids which can be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid.

Basic addition salts can be prepared *in situ* during the final isolation and purification of compounds of this invention by reacting a carboxylic acid-containing moiety with a suitable base such as the hydroxide, carbonate or bicarbonate of a pharmaceutically acceptable metal cation or with ammonia or an organic primary, secondary or tertiary amine. Pharmaceutically acceptable salts include, but are not limited to, cations based on alkali metals or alkaline earth metals such as lithium, sodium, potassium, calcium, magnesium and aluminum salts and the like and nontoxic quaternary ammonia and amine cations including ammonium, tetramethylammonium, tetraethylammonium,

methylammonium, dimethylammonium, trimethylammonium, triethylammonium, diethylammonium, and ethylammonium among others. Other representative organic amines useful for the formation of base addition salts include ethylenediamine, ethanolamine, diethanolamine, piperidine, piperazine and the like.

The proton pump inhibitors disclosed herein are not enteric-coated. By contrast, the commercially available proton pump inhibitors for oral administration are enteric-coated. The presently commercially available form of lansoprazole is PREVACID, a delayed release capsule available from TAP Pharmaceuticals, Inc. The delayed-release capsules contain enteric-coated lansoprazole, wherein the enteric coating is polymeric. Typical enteric coatings are made of cellulose acetate phthalate, hydroxypropylmethylcellulose phthalate, hydroxymethylcellulose acetate succinate, and methacrylic acid/acrylic acid copolymer (EUDRAGIT), among others.

The onset of action of a conventional proton pump inhibitor is about 1.5 to 2 hours. The presence of the enteric coating further delays this onset. Since the present compositions do not include enteric coatings, and do contain a fast-acting acid neutralizer, the length of time for onset of action is reduced. Therefore, the present compositions are advantageous in that they are fast-acting formulations.

As indicated above, the amount of the combination of the carbonate and bicarbonate salts does not depend upon the amount of the proton pump inhibitor utilized. However, the dosage range of the non-enteric coated proton pump inhibitor can range from approximately 0.5 mg/day to approximately 100 mg/day. The standard daily dosage is typically 10-60 mg non-enteric coated proton pump inhibitor, administered as a tablet, suspension or solution.

The Methods

The pharmaceutical composition including the non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier can be used for the treatment of various gastro-intestinal conditions.

The phrase "gastric acid disorders" as used herein includes active duodenal ulcers, gastric ulcers, gastro-esophageal reflux disease (GERD), severe erosive esophagitis, poorly responsive systematic GERD, and pathological hyper-secretory conditions such as Zollinger Ellison Syndrome, among others. Gastric acid disorders are those disorders caused by imbalances between acid and pepsin production, called aggressive factors, and mucus, bicarbonate, and prostaglandin production, called defensive factors.

The phrase "therapeutically effective amount" of the compound of the invention as used herein means a sufficient amount of the compound to treat disorders, at a reasonable benefit/risk ratio applicable to any medical treatment. It will be understood, however, that the total daily usage of the compounds and compositions of the present invention will be decided by the attending physician within the scope of sound medical judgement. The specific therapeutically effective dose level for any particular patient will depend upon a variety of factors including the disorder being treated and the severity of the disorder; activity of the specific compound employed; the specific composition employed; the age, body weight, general health, sex and diet of the patient; the time of administration, route of administration, and rate of excretion of the specific compound employed; the duration of the treatment; drugs used in combination or coincidental with the specific compound employed; and like factors well known in the medical arts. For example, it is well within the skill of the art to start doses of the compound at levels lower than required to achieve the desired therapeutic effect and to gradually increase the dosage until the desired effect is achieved.

The non-enteric coated proton pump inhibitor is administered and dosed in accordance with good medical practice, taking into account the clinical condition of the individual patient, the site and method of administration, scheduling of administration, and other factors known to medical practitioners. The 'therapeutically effective amount" for purposes herein thus can readily be determines by such considerations as are known in the art. The amount must be effective to achieve improvement, including but not limited to, raising of gastric pH, reduced gastrointestinal bleeding, reduction in the need for blood

transfusion, improved survival rate, more rapid recovery, or improvement or elimination of symptoms and other indicators as are selected as appropriate measures by those skilled in the art.

The phrase "pharmaceutically acceptable carrier" as used herein refers to a non-toxic compound such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol or sorbitol among others.

The non-enteric coated proton pump inhibitor and combination of carbonate and bicarbonate salts can be administered in either solid or liquid dosage forms. A solid dosage form is illustrated in Example 4, and a liquid dosage form is illustrated in Example 5.

Liquid dosage forms for oral administration include pharmaceutically acceptable emulsions, solutions, suspensions, syrups and elixirs. In addition to the active compounds, the liquid dosage forms may contain inert diluents commonly used in the art such as, for example, water or other solvents, solubilizing agents and emulsifiers such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, dimethyl formamide, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofurfuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan and mixtures thereof.

Besides inert diluents, the oral compositions may also include adjuvants such as wetting agents, emulsifying and suspending agents, sweetening, flavoring and perfuming agents.

In the method of the present invention, the non-enteric coated proton pump inhibitor can be administered in various ways. The formulations can be made more palatable by adding flavorings such as chocolate, root beer, and others.

Additionally, the present invention can be manufactured by utilizing a micronized non-enteric coated proton pump inhibitor in place of the granules or powder in place of granules. Micronization is utilized in order to produce a particle having a smaller diameter. Micronization is the process by which solid

drug particles are reduced in size. Since the dissolution rate is directly proportional to the surface area of the solid, and reducing the particle size increases the surface area, reducing the particle size increases the dissolution rate.

Although micronization results in increased surface area causing particle aggregation, which can negate the benefit of micronization and is an expensive manufacturing step, it does have the significant benefit of increasing the dissolution rate of relatively water insoluble drugs, such as omeprazole.

A pharmacological formulation of the non-enteric coated proton pump inhibitor utilized in the present invention can be administered orally to the patient.

These Examples are presented to describe preferred embodiments and utilities of the invention and are not meant to limit the invention unless otherwise stated in the claims appended hereto.

Example 1

To illustrate the superiority of carbicarb solution over sodium bicarbonate solution, the comparative amounts of gas produced by each was studied. To quantify the gas produced by the neutralization of simulated gastric fluid (SGF) by carbicarb and by sodium bicarbonate *in vitro*, a standard CO_2 assay technique was utilized (see USP 24 -NF 19 Beta, The United States Pharmacopeia 2000, p. 306)

Aqueous solutions to be tested were made up from starting materials sodium carbonate, (anhydrous, available from Mallinckrodt) and sodium bicarbonate (available from Mallinckrodt). An 8.4% sodium bicarbonate solution and an 8.4% carbicarb solution (containing equimolar amounts of sodium bicarbonate and sodium carbonate) were tested as follows.

The specimen gas was generated by reacting either 450 mL simulated gastric fluid (SGF) with 50 mL of the carbicarb solution; or by reacting 45 ml of simulated gastric fluid with 5 ml of sodium bicarbonate solution in a 500 mL Erlenmeyer flask. The volume of reactants was reduced in the latter case,

otherwise the volume of gas generated was too large to be determined in the Orsat Apparatus.

To make Simulated Gastric Fluid (SGF) 1 g sodium chloride was transferred to a 500-mL volumetric flask. After adding 1.6 g pepsin, 25 mL 2 N hydrochloric acid was added and swirled to mix. The resultant solution could then be diluted to the appropriate volume with water.

The amount of gas generated in a twenty-minute time period was measured in an Orsat Glass Vapor Absorption Apparatus, by the standard assay technique. Two tests were run for each solution. The volume of CO_2 generated was calculated from the difference in the initial volume of gas produced (ml) and the final volume of gas remaining (ml).

Table 1 demonstrates that, on average, there was a fourteen-fold reduction in the total gas generated and a two-fold reduction in the volume of CO_2 generated in the SGF-carbicarb reaction compared to the SGF-sodium bicarbonate reaction.

Table 1

Volumes of total gas and carbon dioxide generated by the neutralization of simulated gastric fluid (SGF) with carbicarb and sodium bicarbonate

Test Solution	Replicate No.	Initial Gas Volume (mL)	Residual Gas Volume (mL)	Volume of CO_2 (mL)
450 mL SGF and 50 mL 8.4% carbicarb solution	1	60.0	39.0	21.0
450 mL SGF and 50 mL 8.4% carbicarb solution	2	62.0	38.5	23.5
45 mL SGF and 5 mL 8.4% sodium bicarbonate solution	1	93.0	90.1	2.9
45 mL SGF and 5 mL 8.4% sodium bicarbonate solution	2	82.0	76.7	5.3
450 mL SGF and 50 mL 8.4% sodium bicarbonate solution	1	930.0	901.0	29.0
450 mL SGF and 50 mL 8.4% sodium bicarbonate solution	2	820.0	767.0	53.0

Example 2

To determine and compare the gastric acid neutralizing capacity of sodium bicarbonate solution to carbicarb solution, the following experiment was performed.

Aqueous solutions to be tested were made up from starting materials sodium carbonate, (anhydrous, available from Mallinckrodt) and sodium bicarbonate (available from Mallinckrodt). An 8.4% sodium bicarbonate solution and an 8.4% carbicarb solution (containing equimolar amounts of sodium bicarbonate and sodium carbonate) were tested as follows.

50 mL simulated gastric fluid (SGF, prepared according to the procedure described in Example 1) was pipetted into an Erlenmeyer flask. Four drops of methyl red, then four drops of phenolphthalein were then added to the flask. The pH of solution was monitored with a pH electrode. The solution to be tested was added to a 5-mL buret. The gastric media in the flask was then titrated with the test solution to an endpoint within 0.2 pH units of pH 6.5 (as indicated by the color change and pH reading). Then, titration was resumed, to an endpoint within 0.2 pH units of pH 8.0 (as indicated by the color change and pH reading).

The endpoint was reached with the addition of 4.71 mL of sodium bicarbonate into the gastric media (Table 2). Similarly, the endpoint was reached with the addition of 3.32 mL of carbicarb solution into the gastric media (Table 2). Direct comparison of the two titrations (Table 2) shows that more of the sodium bicarbonate solution (at the same concentration) was required for the neutralization of the simulated gastric fluid. Thus, in the stomach, less carbicarb would be required to neutralize a given amount of gastric fluid.

Table 2

Neutralization of the Simulated Gastric Fluid Acidity by Carbicarb and Sodium Bicarbonate Solutions

	Volume of Acid Neutralizer Solution Required (ml)	
pH of simulated gastric fluid after adding neutralizer	8.4% Carbicarb solution	8.4% Sodium Bicarbonate solution
1.2	0	0
2.0	2.57	3.47
3.0	3.05	4.09
4.0	3.13	4.19
5.0	3.19	4.27
6.0	3.26	4.48
7.0	3.40	5.00
8.0	3.53	6.20

Example 3

Lansoprazole degrades in acid and is stable in base. This study was performed to determine 1) how quickly lansoprazole degrades in simulated gastric fluid (SGF); and 2) whether a high pH-buffering agent (carbicarb which is an equimolar mixture of sodium carbonate and sodium bicarbonate) could be used to retard the degradation of lansoprazole in SGF. All the experiments were conducted at room temperature (22°C ± 2°C).

The PPI test sample included lansoprazole (30 mg); mannitol (60 mg), meglumine (30 mg) and sodium hydroxide (3 mg).

First, 50.0 mL simulated gastric fluid (SGF, prepared according to the procedure described in Example 1), the PPI test sample and a stir bar were added to each of 6 separate 100-mL beakers labeled (consecutively) as 0, 5, 15, 30, 45, and 60 minutes. Then 5.0 mL 2 N sodium hydroxide solution was added

to the 0-minutes beaker with mixing. To each of the 5 remaining beakers, 10.0 mL of 8.4% carbicarb solution was added and stirred to mix. At the appropriate time interval (corresponding to the individual beaker numbers), 5.0 mL 2 N sodium hydroxide solution was added to stop the reaction. A portion of the resulting solution was diluted with pH 10 diluent. 10 µL of the resulting solution was then injected into the chromatographic system for assay.

The results are shown in Table 3. At 60 minutes, 98% of the drug that was reconstituted with water had degraded. In comparison, only 3.5 % of the drug that was constituted with carbicarb solution had degraded.

Lansoprazole, when administered with carbicarb into simulated gastric fluid (SGF), was stable for at least 60 minutes (< 5% degradation). Carbicarb neutralizes the acidity of simulated gastric fluid (SGF), thereby ensuring the stability and hence clinical utility of lansoprazole.

Table 3

The stability of lansoprazole with and without carbicarb in simulated gastric fluid (SGF).

	% labeled amount of lansoprazole remaining	
Time in SGF (minutes)	Sample in water	Sample in carbicarb solution
0	99.5	98.0
5	39.9	96.7
15	10.1	97.4
30	4.1	95.8
45	2.7	94.4
60	2.0	96.5

Example 4

Granular formulations of lansoprazole, including carbicarb were also made and tested. The stability of the granular formulations was tested according to the procedure of Example 3. The granular formulations of lansoprazole for this example were prepared as follows.

60 gm sucrose (Superior coffee, Bensenville, IL) was dissolved in water (HPLC grade, Fisher Scientific, Pittsburgh, PA) with gentle heating to form a 60

% solution. Then 46.93 gm of sodium carbonate (Fisher Scientific, Pittsburgh, PA) and 37.17 gm of sodium bicarbonate (Fisher Scientific, Pittsburgh, PA) were mixed together thoroughly. Subsequently, 35 gm of this mixture (carbicarb), 7.5 gm lactose and 1.5 gm lansoprazole (Takeda Chemical Industries, Osaka, Japan) were transferred to a mortar and mixed vigorously.

6 ml of the 60 % sucrose solution was gradually added to the mortar while mixing with a pestle to form a coherent, wetted mass. This coherent mass was passed through a 10-mesh screen and the resulting granules were dried at 50°C for 12 hours.

Upon testing by the procedure described in Example 3, the results indicated that lansoprazole, when formulated with carbicarb as granules, was stable in simulated gastric fluid for at least 60 minutes.

Example 5

The granular formulation formed according to the procedure of Example 4 was mixed with water to form a suspension for oral administration, as follows.

The coherent mass containing lansoprazole, carbicarb, lactose and sucrose solution was prepared as described above, in Example 3. This coherent mass was passed through a 20-mesh screen and the resulting granules were dried at 50°C for 12 hours. Granules containing 30-mg lansoprazole were transferred to an amber color container along with and an equal weight of flavor granules.

10 ml of water ((HPLC grade, Fisher Scientific, Pittsburgh, PA) was added to the container with gentle shaking to reconstitute the suspension. The resulting suspension of lansoprazole was tested for stability in simulated gastric fluid as described earlier in Experiment 3.

As in the previous Example, lansoprazole suspension, when reconstituted from lansoprazole/carbicarb granules was stable in simulated gastric fluid for at least 60 minutes.

Additionally, the granules prepared in Examples 4 and 5 were kept at 22°C for 21 days in closed containers. They were then tested for potency and the presence of related substances; and lansoprazole in the formulations was

found to be stable at the conclusion of the study.

All references cited are hereby incorporated by reference.

The present invention is illustrated by way of the foregoing description and examples. The foregoing description is intended as a non-limiting illustration, since many variations will become apparent to those skilled in the art in view thereof. It is intended that all such variations within the scope and spirit of the appended claims be embraced thereby.

Changes can be made in the composition, operation and arrangement of the method of the present invention described herein without departing from the concept and scope of the invention as defined in the following claims:

Claims

We claim:

1. A method for treating gastric acid disorders comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of at least one non-enteric coated proton pump inhibitor in a pharmaceutically acceptable carrier;

wherein said pharmaceutically acceptable carrier includes a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal.

2. The method of claim 1 wherein said Group IA metal of said bicarbonate salt is sodium.

3. The method of claim 1 wherein said Group IA metal of said carbonate salt is sodium.

4. The method of claim 1 wherein said Group IA metal of said bicarbonate salt is potassium.

5. The method of claim 1 wherein said Group IA metal of said carbonate salt is potassium.

6. The method of claim 1 wherein said non-enteric coated proton pump inhibitor is a substituted benzimidazole or pharmaceutically acceptable salt thereof.

7. The method of claim 6 wherein said substituted benzimidazole is lansoprazole or a pharmaceutically acceptable salt thereof.

8. The method of claim 1 wherein the molar ratio of said bicarbonate salt of said Group IA metal to said carbonate salt of said Group IA metal is one

to one.

9. The method of claim 2 wherein said bicarbonate salt of said Group IA metal is sodium bicarbonate.

10. The method of claim 3 wherein said carbonate salt of said Group IA metal is sodium carbonate.

11. The method of claim 9 wherein said pharmaceutically acceptable carrier contains from about 125 mg to about 1000 mg of sodium bicarbonate.

12. The method of claim 10 wherein said pharmaceutically acceptable carrier contains from about 125 mg to about 1000 mg of sodium carbonate.

13. A method for treating gastric acid disorders comprising the step of administering to a patient in need of such treatment a therapeutically effective amount of non-enteric coated lansoprazole or a pharmaceutically acceptable salt thereof in a pharmaceutically acceptable carrier;

wherein said pharmaceutically acceptable carrier includes an equimolar ratio of sodium carbonate to sodium bicarbonate.

14. The method of claim 13 wherein said pharmaceutically acceptable carrier contains from about 125 mg to about 1000 mg of sodium carbonate, and from about 125 mg to about 1000 mg of sodium bicarbonate.

15. A pharmaceutical composition comprising:

at least one non-enteric coated proton pump inhibitor

in a pharmaceutically acceptable carrier;

wherein said pharmaceutically acceptable carrier includes a bicarbonate salt of a Group IA metal and a carbonate salt of a Group IA metal.

16. The composition of claim 15 wherein said Group IA metal of said bicarbonate salt is sodium.

17. The composition of claim 15 wherein said Group IA metal of said carbonate salt is sodium.

18. The composition of claim 15 wherein said Group IA metal of said bicarbonate salt is potassium.

19. The composition of claim 15 wherein said Group IA metal of said carbonate salt is potassium.

20. The composition of claim 15 wherein said non-enteric coated proton pump inhibitor is a substituted benzimidazole or pharmaceutically acceptable salt thereof.

21. The composition of claim 20 wherein said benzimidazole is lansoprazole or a pharmaceutically acceptable salt thereof.

22. The composition of claim 15 wherein the molar ratio of said bicarbonate salt of said Group IA metal to said carbonate salt of said Group IA metal is one to one.

23. The composition of claim 16 wherein said bicarbonate salt of said Group IA metal is sodium bicarbonate.

24. The composition of claim 17 wherein said carbonate salt of said Group IA metal is sodium carbonate.

25. The composition of claim 15 wherein said pharmaceutically acceptable carrier contains from about 125 mg to about 1000 mg of sodium carbonate and from about 125 mg to about 1000 mg of sodium bicarbonate.

26. A non-enteric coated lansoprazole composition consisting essentially of:

a) lansoprazole without enteric coating;

b) a bicarbonate salt of a Group IA metal; and

c) a carbonate salt of a Group IA metal.

27. The composition of claim 26 wherein said bicarbonate salt of said Group IA metal is sodium bicarbonate.

28. The composition of claim 26 wherein said carbonate salt of said Group IA metal is sodium carbonate.

29. The composition of claim 26 having from about 125 mg to about 1000 mg of sodium carbonate, and from about 125 mg to about 1000 mg of sodium bicarbonate.

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(19) (CA) **CANADIAN PATENT** (12)

(54) Pyridyl-N-Oxide Intermediates for the Preparation of Omeprazole

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(21) APPLICATION No. 431,863

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(30) PRIORITY DATE Sweden (8204879-4) 820826

No. OF CLAIMS 13 - NO DRAWING

Canada

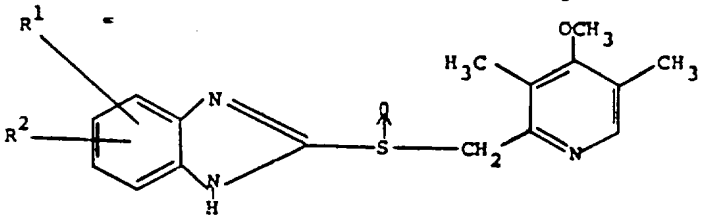
DESCRIPTION

Field of the invention

The present invention relates to novel chemical intermediates, a process for their preparation, and their use in the preparation of pharmacologically active substances.

Background of the invention

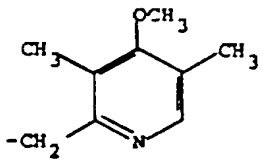
Compounds of the general formula (i) wherein R^1 and R^2 are the same or different and are each selected from the group consisting of hydrogen, alkyl, halogen, carbomethoxy, alkoxy and alkanoyl have been disclosed in e.g. European patent No. 0005 129 as useful therapeutical compounds. One of these compounds, known under the generic name omeprazole (R^1 = = 5-OCH_3, R^2 = H)



(i)

is being developed as a gastric acid secretion inhibiting drug. It can also be used for providing gastrointestinal cytoprotective effects in mammals and man.

It is important to obtain simple and efficient intermediates and routes of synthesis for omeprazole and, in a more general sense, for therapeutically active compounds such as benzimidazole derivatives containing the pyridylmethyl moiety



(ii)

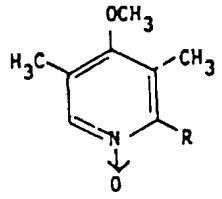
The present invention provides novel compounds which are useful as intermediates in the preparation of therapeutically active compounds such as benzimidazole derivatives which contain a pyridylmethyl radical of the formula (ii), and methods for the preparation of such compounds.

Prior art

Substituted benzimidazoles containing a pyridine radical of the formula (ii) are disclosed i.a. in European patent 0005 129. A problem with these compounds is their stability characteristics. Upon storage without any special precautions being taken, they are degraded at a rate which is higher than desired. E.g. by storage of omeprazole, which is a substituted benzimidazole disclosed in the patent cited above, at accelerated conditions, that is at +37°C and at a relative humidity of 80% for a period of 6 months, about 6% of the substance is converted to degradation products.

Detailed description of the invention

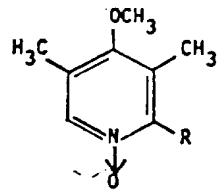
It has been found according to the present invention that the compounds of the formula



I

wherein R is H or CH_3, are novel and useful intermediates in the preparation of pharmaceutically useful compounds, e.g. substituted benzimidazoles of the general formula (i). The compounds of the formula I are the products obtained from the preceding nitration reaction (see preparation below), for which the N-oxide form may be considered necessary, and the following substitution reaction in which the pyridine N-oxide form is very advantageous considering the yields.

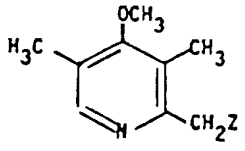
In addition, the N-oxide state of the compounds of the formula I is very advantageous for the subsequent conversion to the 2-hydroxymethylpyridine (procedures A and B). Direct hydroxymethylation of the corresponding non-oxidized pyridines



I

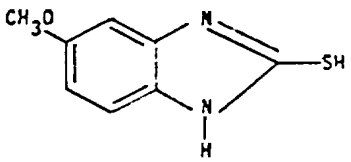
only gives low yields (<20%).

B. The compounds of the formula I may ~~advantageously~~ advantageously be prepared by processing both the nitration step and the substitution step without isolation of the intermediate nitro-pyridine. Furthermore they are stable and can be stored in bulk form. For example, the compounds according to the invention of the formula I are useful as intermediates in the preparation of the corresponding 2-hydroxymethylpyridine and reactive derivatives thereof of the formula

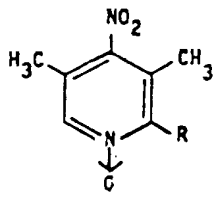


(iii)

or a salt thereof, in which formula Z is a hydroxy group or reactive esterified hydroxy group, e.g. halogen such as Cl and p-toluenesulfonyl used for the preparation of e.g. omeprazole. The reactive intermediate of the formula (iii) is then reacted in known manner with a benzimidazole derivative of the formula



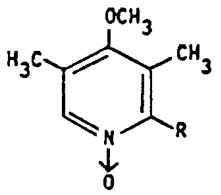
(iv)



IV

wherein R has the meaning given above whereafter

b) the compound of the formula IV is directly reacted with methoxide to give the desired end product of the formula



I

wherein R is H or CH_3.

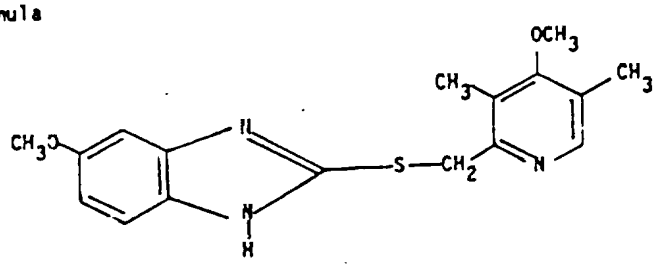
The reaction conditions for the steps a) and b) are suitably the following.

For reaction a), ordinary nitration conditions, i.e., a mixture of conc. sulfuric acid and nitric acid of different concentrations are used. Mixtures containing organic solvents such as acetic acid and nitromethane may also be used.

For reaction b) a solution of methoxide anion in methanol is preferably used. Methoxide salts in inert solvents such as toluene may also be used. A solution of methoxide in methanol can be prepared from sodium hydroxide and methanol.

The utilization of the compounds I in the preparation of reactive derivatives of corresponding 2-hydroxymethylpyridine can be carried out as illustrated below:

whereafter oxidation in known manner of the reaction product of the formula



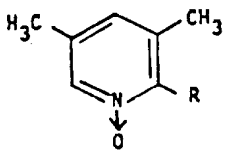
(V)

yields omeprazole. A preferable method of preparing omeprazole is to use a compound with the general formula I, wherein R is H as an intermediate. The most preferable method of preparing omeprazole is to use a compound, wherein R is CH_3 as an intermediate.

The present invention also relates to a process for the preparation of the compounds of the formula I.

The compounds of the invention of the formula I are prepared according to the invention by

a) reacting a compound of the formula



II

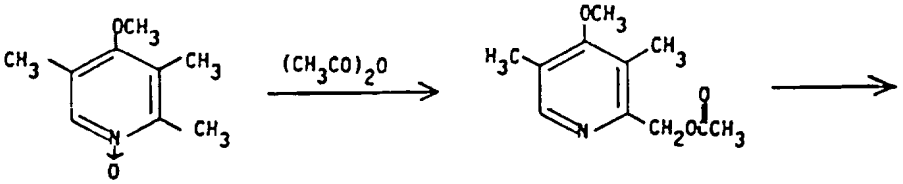
wherein R is H or CH_3,
with a nitrating agent such as nitric acid

HNO_3

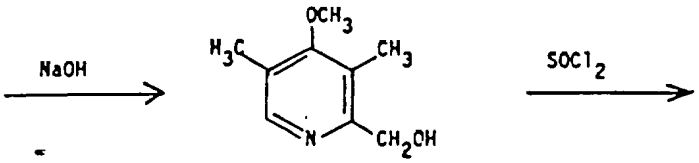
III

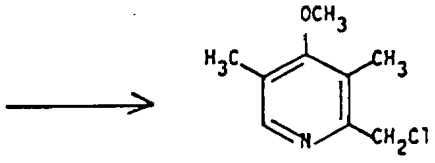
to the formation of a compound of the formula

A. Procedure useful for the preparation of a compound of the formula (iii) utilizing a compound of the formula I wherein R is CH_3:



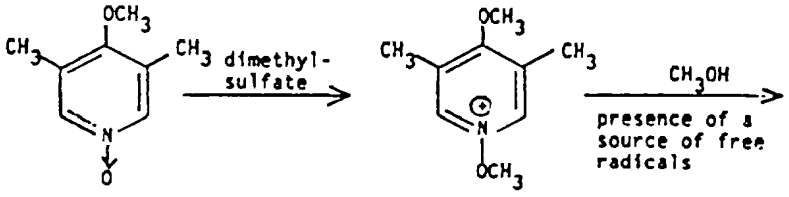
(I)



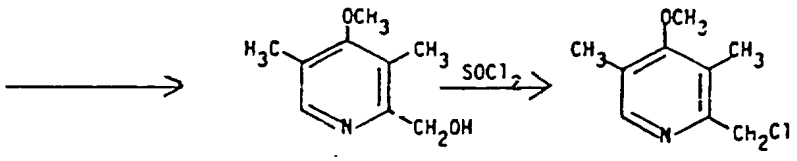


(iii)

B. Procedure useful for the preparation of a compound of the formula (iii) utilizing a compound of the formula I wherein R is H:



(I)



(iii)

Suitable sources of free radicals are e.g. $(NH_4)_2S_2O_8$ or other salts of persulfuric acid.

The compound of the formula (iii) thus obtained, or a salt thereof, is thereafter in known manner as described in the prior art reacted with the desired benzimidazole derivative (iv) as described above.

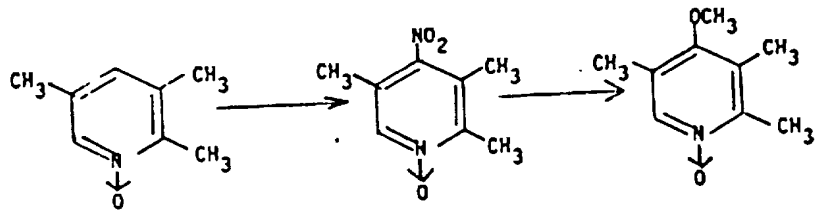
The invention is illustrated by the following examples.

Example 1. Preparation of 2,3,5-trimethyl-4-methoxypyridine-N-oxide

2,3,5-trimethyl-pyridine-N-oxide (1457 g, 10 moles) was dissolved in conc. H_2SO_4 (1200 ml, 22.08 moles) in a 50 litres reaction vessel. A nitration solution (1750 ml, 32.2 moles conc. H_2SO_4 and 2065 ml, 29.84 moles 65% HNO_3) was added at 90°C during 1 hour. The solution was stirred at 90° for 1.5 hours and thereafter cooled to 30°C. The pH of the reaction mixture was then adjusted by adding 10M NaOH (11.65 litres, 116.5 moles) during cooling with water so that the temperature was kept below 40°C. The NaOH was added during about 2 hours. Thereafter CH_2Cl_2 (25 litres) was added and the mixture stirred vigorously for 30 minutes. The phases formed were separated and the CH_2Cl_2-phase was transferred to a 100 litres reaction vessel. The water phase was discarded. The methylenechloride was distilled off. To the remainder was added 15 l of toluene which was then distilled off under reduced pressure, followed by another 15 l portion of toluene which was also removed by distillation. 8 litres of methanol was added and the mixture heated to boiling temperature. A solution of NaOH (595 g, 14.9 moles) in CH_3OH (16 litres) was added during about 1.5 hours. The reaction mixture obtained was cooled and its pH adjusted to 8 using conc. H_2SO_4 (250 ml, 4.6 moles). Remaining methanol was distilled off and CH_2Cl_2 (20 litres) was added to the remainder. The mixture was stirred for about 30 minutes and inorganic salts were filtered off and washed with CH_2Cl_2. The fil-

trates obtained were pooled and evaporated, yielding 1287 g of 2,3,5-trimethyl-4-methoxy-pyridine-N-oxide with a purity of 89%. The identity of the reaction product was confirmed with ^{1}H and ^{13}C NMR. ^{1}H-NMR: $\delta(COCl_3)$ 2.22(s,3H),2.27(s,3H),2.51(s,3H),3.81(s,3H),8.18(s,1H).

The reaction sequence is:



The 2,3,5-trimethylpyridine-N-oxide used as starting material was prepared as follows.

Preparation of 2,3,5-trimethyl-pyridine-N-oxide.

To a 100 litres reaction vessel was added 2,3,5-trimethyl-pyridine (10.9 kg, 89.2 moles) and acetic acid (30 litres). The temperature was raised to 90°C. The mixture was stirred for 3 hours and thereafter cooled to 60°C, whereafter H_2O_2 (35% solution, 3122 ml, 35,67 moles) was added during 1 hour. The temperature was then raised to 90°C. The reaction mixture was stirred overnight. After cooling to 40°C an additional amount of H_2O_2 solution (936 m^3, 10.7 moles) was added during 1 hour. The temperature was then raised to 90°C. The reaction mixture was stirred for 3 hours and was allowed to stand without heating overnight.Excess of acetic acid was distilled off under vaccum. To the remainder was added NaOH (10M) until pH 10. CH_2Cl_2 (10 litres) was added and the resulting mixture was stirred vigorously. The CH_2Cl_2 phase was separated and the water phase was extracted twice with CH_2Cl_2 (10 litres). The combined CH_2Cl_2 - phases were dried over $MgSO_4$ and filtrated. The filtrate was evaporated yielding 2,3,5-trimethyl-pyridine-N-oxide (11920 g, 94% purity). The identity of the product was confirmed with ^{1}H and ^{13}C NMR.

Example 2. Preparation of 3,5-dimethyl-4-methoxy-pyridine-N-oxide.

3,5-dimethyl-pyridine-N-oxide (3500 g, 28.5 moles) was dissolved in conc. H_2SO_4 (3500 ml, 64.4 moles). The solution was cooled to 90°C and nitration solution (5 l, 91.5 moles, conc. H_2SO_4 and 5.9 l, 85 moles 65% HNO_3) was added during 4 hours at 90°C. The solution was stirred at 90°C over night. The solution was cooled to 30°C and neutralized with 10M NaOH (36 l, 360 moles) during 4 hours and the temperature kept below 30°C. Acetonitrile (35 litres) was added and the mixture stirred vigorously for 30 minutes. The acetonitrile layer was separated. The extraction procedure was repeated with 15 l of acetonitrile, and the combined acetonitrile were extracted with water (10 l at 60°C). The upper layer was collected and evaporated at reduced pressure (bp 30-55°C/130 mm Hg). Toluene (10 l) was added and remaining water was thoroughly removed by azeotropic distillation at reduced pressure (bp 55-65°C/130 mm Hg). Methylalcohol (7 l, 173 moles) was added and the mixture was heated to reflux temperature. A solution of NaOH (1138 g, 28.45 moles) in 30 litres methylalcohol was added over a period of 15 hours. The reaction mixture was cooled and pH adjusted to 9 using conc. HCl (1200 ml, 14 moles). Remaining methanol was evaporated. The residue was cooled and CH_2Cl_2 (30 l) and activated carbon (50 g)were added. The mixture was stirred for 30 minutes, filtered and the residue washed with CH_2Cl_2. The filtrates were evaporated. The solid product was washed with petroleum ether, (5 litres bp 60-80°C) at 50°C for 30 minutes and filtered. This procedure was repeated once. The product was dried at reduced pressure. Yield 2400 g 3,5-dimethyl-4-methoxypyridine-N-oxide with a purity of 90%. The identity of the product was confirmed with ^1H- and ^{13}C-NMR. ^1H-NMR: $\delta(COCl_3)$ 2.23(s,6H),3.81(2,3H), 8.03(s,2H).

The 3,5-dimethyl-pyridine-N-oxide used as starting material was prepared as follows.

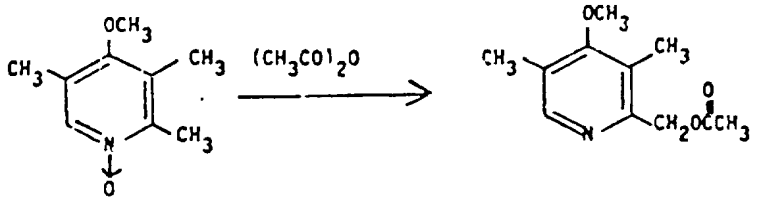
3,5-lutidine (15 kg, 140.2 moles) was dissolved in acetic acid (48 l) at 60°C. Hydrogen peroxide (8430 ml, 98 moles) was added during 3 hours. The solution was heated to 90°C and kept at this temperature for 3 hours. The reaction mixture was cooled to 60°C and hydrogen peroxide (3500 ml, 41 moles) was added during 1 hour. The temperature was raised

to 90°C and kept there for 16 hours. The reaction mixture was evaporated at reduced pressure (70°C 300 mm Hg). The residue (approx 25 litres) was cooled and pH adjusted to 10 with NaOH-solution (23 litres 10M). Acetonitrile (30 litres) was added and the mixture was stirred for 30 minutes. The sodiumacetate was separated off and washed with 10 l acetonitrile. The liquid phase was evaporated at reduced pressure (55°C, 200 mm Hg). The remaining solution (approx 25 litres) was extracted with CH_2Cl_2 (20 litres and 3 x 5 litres). The combined organic layers were dried over $MgSO_4$, filtrated and evaporated at reduced pressure (50°C 200 mm Hg). When all CH_2Cl_2 had distilled off unreacted 3,5-lutidine was evaporated at 75°C, 8 mm Hg. Yield 14940 g of 3,5-dimethylpyridine-N-oxide. The identity was confirmed with ^1H and ^{13}C NMR.

The conversion of the compounds of the formula I to 3,5-dimethyl-4-methoxy-2-hydroxymethylpyridine can be carried out according to Procedure A and Procedure B as described above and exemplified below.

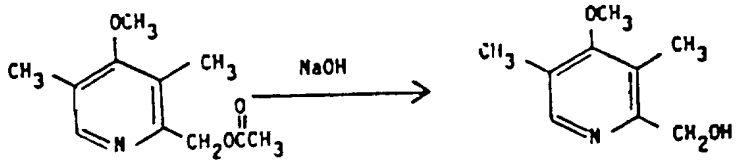
Procedure A:

step 1:



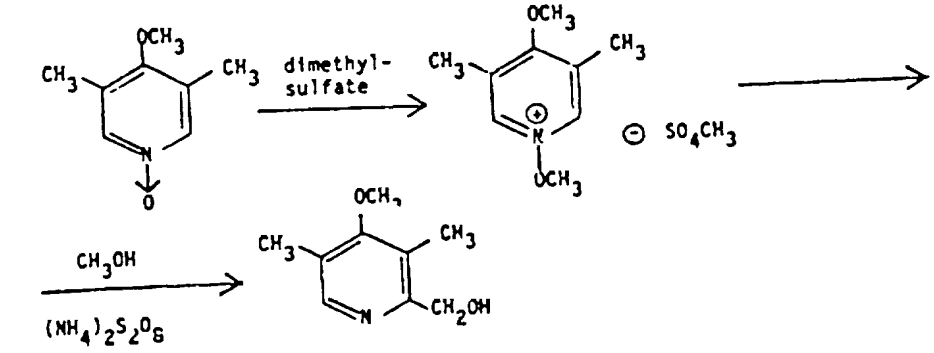
2,3,5-dimethyl-4-methoxypyridine-N-oxide (1268 g. 6.75 moles) obtained in Example 1, dissolved in acetic acid (740 ml), was added dropwise to $(CH_3CO)_2O$ (2140 ml) heated to 90°C. The heating was discontinued during the addition. The temperature rose to 130°C. Thereafter the reaction solution was stirred for 1 hour and then cooled to 80°C whereafter CH_3OH (2460 ml) was added. The reaction solution was evaporated and the remainder used directly in step 2.

step 2:



To the remainder from step 1 was added NaOH (3300 ml, 10M). The mixture was refluxed for 5 hours, cooled and extracted with CH_2Cl_2 (8 litres). The phases were separated and the water phase extracted with CH_2Cl_2 (2 x 4 litres). The combined CH_2Cl_2 - phases were dried over $MgSO_4$, refluxed with a few grams of decolorizing carbon and filtrated, yielding 3,5-dimethyl-4-methoxy-2-hydroxy-methylpyridine (941 g). The identity of the product was confirmed with ^1H and ^{13}C NMR.

Procedure B:

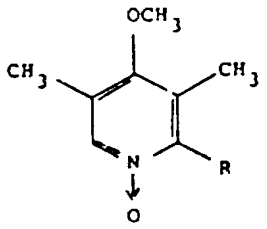


3,5-Dimethyl-4-methoxypyridine-N-oxide (61.2 g) obtained in Example 2 was dissolved in CH_3OH (458 ml). Dimethylsulfate (38 ml 0.4 moles) was added dropwise during 15 minutes and pH adjusted to 5.0 using 10M NaOH. The mixture was stirred for 15 minutes and thereafter refluxed for 1 hour. An additional amount of dimethylsulfate (3.8 ml, 0.04 moles) was added dropwise and the mixture was refluxed for 1.5 hours. Stirring

was continued overnight at room temperature. Thereafter the mixture was heated to reflux and $(NH_4)_2S_2O_8$ (91.2 g, 0.4 mole) dissolved in water (169 ml) was added during 1.75 hours, followed by refluxing for 1.5 hours and stirring at room temperature overnight. Thereafter CH_3OH (452 ml) was added. Precipitated salts were filtered off and discarded. After evaporation of CH_3OH, the remaining water phase (pH 0.6) was adjusted to pH 10.0 using 10M NaOH (145 ml). The water phase was extracted three times with CH_2Cl_2. The combined CH_2Cl_2 phases were dried over Na_2SO_4, evaporated and dried, yielding 3,5-dimethyl-4-methoxy-2-hydroxymethylpyridine (44.2 g). The identity of the product was confirmed with ^1H and ^{13}C NMR and the purity checked with gas chromatography.

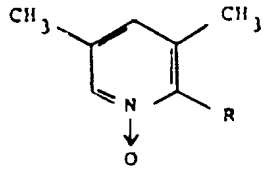
THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of a compound of the formula



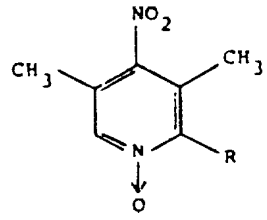
I

wherein R is hydrogen or methyl, which process comprises nitrating a compound of the formula



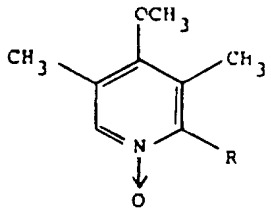
II

to form a compound of the formula



IV

in which formulas R is hydrogen or methyl, and reacting the compound of the formula IV thus obtained with a methoxide to give a compound of the formula



I

in which formulas R is hydrogen or methyl.

2. A process according to claim 1 wherein the reaction with methoxide is carried out in methanol.

3. A process according to claim 1 wherein the nitration is carried out by reaction with nitric acid.

4. A process according to claim 3 wherein the nitric acid is in admixture with sulphuric acid.

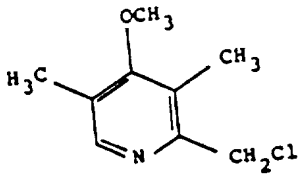
5. A process according to claim 1 wherein R is methyl.

6. A process according to claim 1 wherein R is hydrogen.

7. A process according to claim 1 wherein R is methyl and the obtained compound of formula I is subjected to reaction with acetic anhydride followed by alkali to convert the methyl group in the 2-position into a hydroxymethyl group.

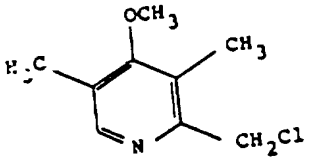
8. A process according to claim 1 wherein R is hydrogen and the obtained compound of formula I is subjected to reaction with dimethyl sulphate followed by reaction with methanol in the presence of a source of free radicals to insert in the 2-position a hydroxymethyl group.

9. A process according to claim 7 or 8 which comprises the further step of reacting the 2-hydroxymethyl compound with a chlorinating agent to obtain a compound of formula (iii)



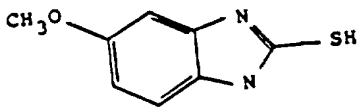
(iii)

10. A process according to claim 7 or 8 which comprises the further step of reacting the 2-hydroxymethyl compound with a chlorinating agent to obtain a compound of formula (iii)



(iii)

followed by reaction with a benzimidazole derivative of the formula (iv)



(iv)

and oxidation to yield omeprazole.

11. A compound of formula I as defined in claim 1.

12. A compound of formula I as defined in claim 1 wherein R is methyl.

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13. A compound of formula I as defined in claim 1 wherein R is hydrogen.

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PATENT AGENTS

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